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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/827,498	04/19/2004	Liangjing Chen	6560US	3464

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APPLIED BIOSYSTEMS INC.
2130 WOODWARD STREET
AUSTIN, TX 78744-1832

EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/827,498	CHEN ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *129-175* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *129-131,144-148,152-155,157-162,164-174,* is/are allowed.

6)☒ Claim(s) *132,133,149-151,156,163 and 175* is/are rejected.

7)☒ Claim(s) *134-143* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's cancellation of claims 1, 5-9, 11-28, 84-98, 102-112, 115-125 and 127-128 and the addition of new claims 130-175, in the paper of 9/22/2008, is acknowledged. Claims 129-175 are at issue and are present for examination.

Applicants' arguments filed on 9/22/2008, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 134-143 150 and 151 are objected to because of the following informalities:

Claims 134-143 are objected to in that the recitation "aRNA" should be preceded by its meaning, as disclosed in paragraph 20, as "amplified RNA", followed by "aRNA" in parenthesis the first time it is used.

Claims 150 and 151 are objected to as improperly depending upon claim 129, in that claims 150 and 151 appear to be broader then claim 129 from which they depend.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 132, 133, 149, 156, 163 and 175 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 132 and 133 are indefinite in its recitation "purified" in that it is unclear how "purified" of claim 132 further limits the already "isolated reverse transcriptase" of claim 129. Applicant's specification does not help in alleviating this confusion. Applicants specification (paragraph [0037]) states "Purified genes, nucleic acids, protein and the like are used to refer to these entities when identified and separated from at least one contaminating nucleic acid or protein with which it is ordinarily associated." This definition of "purified" does not further limit "isolated" and thus the use of it in the context of claim 132 is confusing and unclear.

Claim 149 is indefinite in its reference to "the RNase H activity is between about 0.1 and about 25 percent of the wild-type RNase H activity" in that it is unclear and confusing as to what "the wild-type RNase H activity" is in the context of the claim.

Claims 156 and 163 are indefinite in that in is unclear as to the difference between the recited "reverse transcriptase buffer" (claim 156) and a " reaction solution for the reverse transcriptase protein" (claim 163) from the "reverse transcriptase reaction buffer" of claim 154. The basis of the necessary distinction between the recited buffers is to support that claims 154, 163 and 156, all of which are drawn to the kit of claim 152, are not duplicative claims.

Claim 175 is indefinite in that the recitation "one or more further reverse transcriptases" is unclear and confusing. It is not clear as to applicant's intent in this recitation.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 150 and 151 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A similar rejection was stated in the previous office action as it applied to previous claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-128. In response to this rejection applicants cancelled claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-128 and added new claims 150 and 151. While applicants state that the claims are added to essentially reiterate now canceled claims 5-8, 13-28, 84-97, 102-103 and 105-114, applicants have not commented or traversed as to how the rejection relates to the newly added claims. Applicant's comments regarding the previous rejections under 112 first paragraph written descriptions have been considered to the extent that they relate to applicants newly amended claims, however, are not found persuasive in the withdrawal of this rejection.

Claims 150 and 151 are directed to all possible reverse transcriptase proteins comprising SEQ ID NO: 2 with the additional specified mutations of the processivity domain and the nucleotide selection domain. As previously stated the specification, only provides the representative species of the M-MLV reverse transcriptase comprising the amino acid sequence of SEQ ID NO: 2 consisting a mutation at position H638 and F155, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these reverse transcriptases by any identifying structural characteristics or properties other than the activities recited in claims 1, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 150 and 151 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the M-MLV reverse transcriptase comprising the amino acid sequence of SEQ ID NO: 2 consisting of a mutation at position H638 and F155, does not reasonably provide enablement for any hyperactive M-MLV reverse

transcriptase protein comprising a mutation in the processivity domain corresponding to H638 and a mutation in the nucleotide selection domain corresponding to F155. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A similar rejection was stated in the previous office action as it applied to previous claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-128. In response to this rejection applicants cancelled claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-128 and added new claims 150 and 151. While applicants state that the claims are added to essentially reiterate now canceled claims 5-8, 13-28, 84-97, 102-103 and 105-114, applicants have not commented or traversed as to how the rejection relates to the newly added claims. Applicant's comments regarding the previous rejections under 112 first paragraph written description have been considered to the extent that they relate to applicants newly amended claims, however, are not found persuasive in the withdrawal of this rejection.

Claims 150 and 151 are so broad as to encompass any reverse transcriptase protein comprising SEQ ID NO: 2 with the additional specified mutations of the processivity domain and the nucleotide selection domain. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of enzymes broadly encompassed by the claims, including any reverse transcriptase comprising virtually any mutation in the processivity domain and any point mutation in the nucleotide selection domain. The claims rejected under this

section of U.S.C. 112, first paragraph, place limited if any structural limits on the claimed reverse transcriptases. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that M-MLV reverse transcriptase comprising the amino acid sequence of SEQ ID NO: 2 consisting a mutation at position H638 and F155.

As previously stated, while recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any the reverse transcriptase comprising the one or more mutations in the processivity domain and one or more point mutations in the nucleotide selection domain of SEQ ID NO:2, because the specification does not

establish: (A) regions of the protein structure which may be modified without effecting the reverse transcriptase activity; (B) the general tolerance of reverse transcriptase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a reverse transcriptase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the reverse transcriptase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having the claimed reverse transcriptase activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of the reverse transcriptase of SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those reverse transcriptases having the desired biological characteristics is unpredictable and the

experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 150 and 151 are rejected under 35 U.S.C. 102(b) as being anticipated by Ruppert (U.S. Patent No. 5,891,637).

Ruppert teaches the a reverse transcriptase protein comprising SEQ ID NO: 2 further comprising one or more mutations that replace at least one amino acid of the processivity domain and the nucleotide domain selected a valine substituted with an isoleucine residue (See specifically the valine to isoleucine substitution at position 102 of SEQ IS NO: 2 in attached alignment).

Thus Ruppert anticipates claims 150 and 151.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
1/4/2009

/Richard G Hutson/
Primary Examiner, Art Unit 1652